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HIV combi

cobas®

HIV-1 antigen and total antibodies to HIV-1 and HIV-2

REF	Σ	SYSTEM
04860446 190	100	Elecsys 2010 MODULAR ANALYTICS E170 **cobas e** 411 **cobas e** 601 **cobas e** 602

English

Intended use

Immunoassay for the in vitro qualitative determination of HIV-1 p24 antigen and antibodies to HIV-1, including group O, and HIV-2 in human serum and plasma.

The **e**lectro**c**hemi**l**uminescence **i**mmuno**a**ssay "ECLIA" is intended for use on Elecsys and **cobas e** immunoassay analyzers.

Regulatory approval

This assay has been CE marked according to Directive 98/79/EC. Test performance has been established and certified by a Notified Body according to the Common Technical Specifications (CTS) for diagnostic use and for screening of blood donations.

Summary

The human immunodeficiency virus (HIV), the causative agent of Acquired Immunodeficiency Syndrome (AIDS), belongs to the family of retroviruses. HIV can be transmitted through contaminated blood and blood products, through sexual contact or from a HIV infected mother to her child before, during and after birth.

Two types of human deficiency viruses, called HIV-1 and HIV-2, have been identified to date.[1,2,3,4] Various subtypes of the known HI-Viruses have been described, each of which has a different geographical distribution. HIV-1 can be divided into 3 distantly related groups: group M (for main), group N (for non-M, non-O) and group O (for outlier).[5,6] Based on their genetic relationship, at least 9 different subtypes (A to D, F to H, J, K) have been identified within HIV-1 group M.[7] Recombinant HIV-1 viruses consisting of sequences of 2 or even more different subtypes exist and are spreading epidemically.

Antibodies to HIV proteins, indicating the presence of an HIV infection, can be found in the serum usually 6-12 weeks after infection.[8,9] Due to differences in the sequence of immunodominant epitopes, especially in the envelope proteins HIV-1 group M, HIV-1 group O and HIV-2, specific antigens are necessary to avoid failure in the detection of an HIV infection by immunoassays.[9,10] By detecting the HIV-1 p24 antigen in blood specimens of recently infected patients with a high viral load, HIV infection can be detected about 6 days earlier than with traditional antibody assays.[11,12] Anti-HIV antibodies and the HIV-1 p24 antigen can be detected simultaneously using a 4th generation HIV assay. This leads to improved sensitivity and, therefore, a shorter diagnostic window as compared to anti-HIV assays.[13,14]

With the Elecsys HIV combi assay the HIV-1 p24 antigen and antibodies to HIV-1 and HIV-2 can be detected simultanously within one determination. The assay uses recombinant antigens derived from the polymerase and envelope region of HIV-1 (including group O) and HIV-2 to determine HIV-specific antibodies. For the detection of HIV-1 p24 antigen specific monoclonal antibodies are used. The Elecsys HIV combi assay is not a replacement for stand-alone HIV antigen assays. Repeatedly reactive samples must be confirmed according to recommended confirmatory algorithms. Confirmatory tests include Western Blot and HIV RNA tests.

Test principle

Sandwich principle. Total duration of assay: 18 minutes.

- 1st incubation: 30 µL of sample, biotinylated monoclonal anti-p24 antibodies/HIV-specific recombinant antigens/HIV-specific peptides, and monoclonal anti-p24 antibodies/HIV-specific recombinant antigens/HIV-specific peptides labeled with a ruthenium complex[a)] react to form a sandwich complex.
- 2nd incubation: After addition of streptavidin-coated microparticles, the complex becomes bound to the solid phase via interaction of biotin and streptavidin.
- The reaction mixture is aspirated into the measuring cell where the microparticles are magnetically captured onto the surface of the electrode. Unbound substances are then removed with ProCell/ProCell M. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier.
- Results are determined automatically by the software by comparing the electrochemiluminescence signal obtained from the reaction product of the sample with the signal of the cutoff value previously obtained by calibration.

a) Tris(2,2'-bipyridyl)ruthenium(II)-complex ($Ru(bpy)_3^{2+}$)

Reagents - working solutions

The reagent rackpack (M, R1, R2) is labeled as HIVCOM.

M Streptavidin-coated microparticles (transparent cap), 1 bottle, 6.5 mL: Streptavidin-coated microparticles 0.72 mg/mL; preservative.

R1 Anti-p24~, HIV-1/-2-specific recombinant antigens (E. coli)~, HIV-1/-2-specific peptides~biotin (gray cap), 1 bottle, 8 mL: Biotinylated monoclonal anti-p24 antibodies (mouse), biotinylated HIV-1/-2-specific recombinant antigens (E. coli), biotinylated HIV-1/-2-specific peptides > 1.3 mg/L; TRIS buffer 50 mmol/L, pH 7.5; preservative.

R2 Anti-p24~, HIV-1/-2-specific recombinant antigens (E. coli)~, HIV-1/-2-specific-peptides~$Ru(bpy)_3^{2+}$ (black cap), 1 bottle, 8 mL: Monoclonal anti-p24 antibodies (mouse), HIV-1/-2-specific recombinant antigens, HIV-1/-2-specific peptides labeled with ruthenium complex > 1.5 mg/L; TRIS buffer 50 mmol/L, pH 7.5; preservative.

HIVCOM Cal1 Negative calibrator (white cap), 2 bottles (lyophilized) for 1.0 mL each: Human serum, non reactive for anti-HIV-1 and anti-HIV-2.

HIVCOM Cal2 Positive calibrator (black cap), 2 bottles (lyophilized) for 1.0 mL each: Anti-HIV-1 positive human serum (inactivated) in human serum negative for anti-HIV-1 and anti-HIV-2.

Precautions and warnings

For in vitro diagnostic use.

Exercise the normal precautions required for handling all laboratory reagents.

Disposal of all waste material should be in accordance with local guidelines.

Safety data sheet available for professional user on request.

All human material should be considered potentially infectious.

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The negative calibrator (HIVCOM Cal1) has been prepared exclusively from the blood of donors tested individually and shown to be free from HBsAg and antibodies to HCV and HIV.

The testing methods applied were FDA-approved or cleared in compliance with the European Directive 98/79/EC, Annex II, List A.

The serum containing anti-HIV-1 (HIVCOM Cal2) was inactivated using β-propiolactone and UV-radiation.

However, as no inactivation or testing method can rule out the potential risk of infection with absolute certainty, the material should be handled with the same level of care as a patient specimen. In the event of exposure, the directives of the responsible health authorities should be followed.[15,16]

Avoid foam formation in all reagents and sample types (specimens, calibrators and controls).

Reagent handling

The reagents in the kit are ready for use (except for HIVCOM Cal1 and HIVCOM Cal2) and are supplied in bottles compatible with the system.

Calibrators

Carefully dissolve the contents of one bottle by adding exactly 1.0 mL of distilled or deionized water and allow to stand closed for 15 minutes to reconstitute. Mix carefully, avoiding foam formation.

Transfer the reconstituted calibrators into the supplied empty labeled snap-cap bottles.

Elecsys 2010 and **cobas e** 411 analyzers: The reconstituted calibrators should only be left on the analyzers during calibration at 20-25 °C. After use, close the bottles as soon as possible and store at 2-8 °C.

Due to possible evaporation effects, not more than 5 calibration procedures per bottle set should be performed.

MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602 analyzers: Unless the entire volume is necessary for calibration on the analyzers, transfer aliquots of the freshly reconstituted calibrators into empty snap-cap bottles (CalSet Vials). Attach the supplied labels to these additional bottles. Store the aliquots at 2-8 °C for later use.

Perform **only one** calibration procedure per aliquot.

All information required for correct operation is read in from the respective reagent barcodes.

Storage and stability

Store at 2-8 °C.

Do not freeze.

Store the Elecsys reagent kit **upright** in order to ensure complete availability of the microparticles during automatic mixing prior to use.

Stability of the reagent rackpack	
unopened at 2-8 °C	up to the stated expiration date
after opening at 2-8 °C	4 weeks if stored alternately in the refrigerator and on the analyzers (up to 70 hours at 20-25 °C)
on Elecsys 2010 and **cobas e** 411 at 20-25 °C	2 weeks
on MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602	2 weeks

Stability of the calibrators	
lyophilized calibrators	up to the stated expiration date
reconstituted calibrators at 2-8 °C	8 weeks
on Elecsys 2010 and **cobas e** 411 at 20-25 °C	up to 5 hours
on MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602	use only once

Store calibrators **upright** in order to prevent the calibrator solution from adhering to the snap-cap.

Specimen collection and preparation

Only the specimens listed below were tested and found acceptable.

Serum collected using standard sampling tubes or tubes containing separating gel.

Li-heparin, K_3-EDTA and sodium citrate plasma.

Criterion: Correct assignment of negative and positive samples.

Stable for 10 days at 2-8 °C, 3 days at 25 °C, 3 months at -20 °C. The samples may be frozen 6 times.

The sample types listed were tested with a selection of sample collection tubes that were commercially available at the time of testing, i.e. not all available tubes of all manufacturers were tested. Sample collection systems from various manufacturers may contain differing materials which could affect the test results in some cases. When processing samples in primary tubes (sample collection systems), follow the instructions of the tube manufacturer.

Centrifuge samples containing precipitates and frozen samples before performing the assay.

Do not use heat-inactivated samples.

Do not use samples and controls stabilized with azide.

Ensure the samples, calibrators and controls are at 20-25 °C prior to measurement.

Due to possible evaporation effects, samples, calibrators and controls on the analyzers should be analyzed/measured within 2 hours.

Materials provided

See "Reagents – working solutions" section for reagents.

- 2 x 6 bottle labels
- 4 empty labeled snap-cap bottles

Materials required (but not provided)

- REF 05162645190, PreciControl HIV, for 2 x 2 mL each of PreciControl HIV 1, 2 and 3
- REF 11776576322, CalSet Vials, 2 x 56 empty snap-cap bottles
- General laboratory equipment
- Elecsys 2010, MODULAR ANALYTICS E170 or **cobas e** analyzer
- Distilled or deionized water

Accessories for Elecsys 2010 and **cobas e** 411 analyzers:

- REF 11662988122, ProCell, 6 x 380 mL system buffer
- REF 11662970122, CleanCell, 6 x 380 mL measuring cell cleaning solution
- REF 11930346122, Elecsys SysWash, 1 x 500 mL washwater additive
- REF 11933159001, Adapter for SysClean
- REF 11706802001, Elecsys 2010 AssayCup, 60 x 60 reaction vessels
- REF 11706799001, Elecsys 2010 AssayTip, 30 x 120 pipette tips

Accessories for MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602 analyzers:

- REF 04880340190, ProCell M, 2 x 2 L system buffer
- REF 04880293190, CleanCell M, 2 x 2 L measuring cell cleaning solution
- REF 03023141001, PC/CC-Cups, 12 cups to prewarm ProCell M and CleanCell M before use
- REF 03005712190, ProbeWash M, 12 x 70 mL cleaning solution for run finalization and rinsing during reagent change
- REF 03004899190, PreClean M, 5 x 600 mL detection cleaning solution

- REF 12102137001, AssayTip/AssayCup Combimagazine M, 48 magazines x 84 reaction vessels or pipette tips, waste bags
- REF 03023150001, WasteLiner, waste bags
- REF 03027651001, SysClean Adapter M

Accessories for all analyzers:

- REF 11298500316, Elecsys SysClean, 5 x 100 mL system cleaning solution

Assay

For optimum performance of the assay follow the directions given in this document for the analyzer concerned. Refer to the appropriate operator's manual for analyzer-specific assay instructions.

Resuspension of the microparticles takes place automatically prior to use. Read in the test-specific parameters via the reagent barcode. If in exceptional cases the barcode cannot be read, enter the 15-digit sequence of numbers.

MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602 analyzers: PreClean M solution is necessary.

Bring the cooled reagents to approx. 20 °C and place on the reagent disk (20 °C) of the analyzer. Avoid foam formation. The system automatically regulates the temperature of the reagents and the opening/closing of the bottles.

Place the reconstituted calibrators in the sample zone.

All the information necessary for calibrating the assay is automatically read into the analyzer.

After calibration has been performed, store the calibrators at 2-8 °C or discard (MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602 analyzers).

Calibration

Traceability: No internationally accepted standard for anti-HIV-1 and anti-HIV-2 exists.

This method has been standardized against the Human Immunodeficiency Virus Type 1 (HIV-1 p24 Antigen) - 1st International Reference Reagent 1992, code 90/636 - available from NIBSC (National Institute for Biological Standards and Control).

Calibration frequency: Calibration must be performed once per reagent lot using HIVCOM Cal1 and HIVCOM Cal2 and fresh reagent (i.e. not more than 24 hours since the reagent kit was registered on the analyzer).

Renewed calibration is recommended as follows:

- after 1 month (28 days) when using the same reagent lot
- after 7 days (when using the same reagent kit on the analyzer)
- as required: e.g. quality control findings with PreciControl HIV outside the defined limits
- more frequently when this is required by pertinent regulations

Range for the electrochemiluminescence signals (counts) for the calibrators:

Negative calibrator (HIVCOM Cal1):

1600-5600 (Elecsys 2010 and **cobas e** 411 analyzers)

800-3000 (MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602 analyzers)

Positive calibrator (HIVCOM Cal2):

24000-110000 (Elecsys 2010 and **cobas e** 411 analyzers)

18000-90000 (MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602 analyzers)

Quality control

For quality control, use PreciControl HIV.

Controls for the various concentration ranges should be run individually at least once every 24 hours when the test is in use, once per reagent kit, and following each calibration.

The control intervals and limits should be adapted to each laboratory's individual requirements. Values obtained should fall within the defined limits. Each laboratory should establish corrective measures to be taken if values fall outside the defined limits.

If necessary, repeat the measurement of the samples concerned.

Follow the applicable government regulations and local guidelines for quality control.

Note:

For technical reasons re-assigned target values valid only for a specific reagent and control lot combination, must be entered manually on all analyzers (except for the **cobas e** 602 analyzer). Therefore always refer to the value sheet included in the rackpack or PreciControl kit to make sure that the correct target values are used.

When a new reagent or control lot is used, the analyzer will use the original values encoded in the control barcodes.

Calculation

The analyzer automatically calculates the cutoff based on the measurement of HIVCOM Cal1 and HIVCOM Cal2.

The result of a sample is given either as reactive or non-reactive as well as in the form of a cutoff index (signal sample/cutoff).

Interpretation of the results

Samples with a cutoff index < 0.90 are non-reactive in the Elecsys HIV combi test. These samples are considered negative for HIV-1 Ag and HIV-1/-2 specific antibodies and do not need further testing. Samples having a cutoff index in the range ≥ 0.90 to < 1.0 are considered borderline in the Elecsys HIV combi assay.

Samples with a cutoff index ≥ 1.0 are considered reactive in the Elecsys HIV combi assay.

All initially reactive or borderline samples should be redetermined in duplicate with the Elecsys HIV combi assay. If cutoff index values < 0.90 are found in both cases, the samples are considered negative for HIV-1 Ag and HIV-1/-2 specific antibodies.

Initially reactive or borderline samples giving cutoff index values of ≥ 0.90 in either of the redeterminations are considered repeatedly reactive. Repeatedly reactive samples must be confirmed according to recommended confirmatory algorithms. Confirmatory tests include Western Blot and HIV RNA tests.

Limitations - interference

The assay is unaffected by icterus (bilirubin < 222 µmol/L or < 13 mg/dL), hemolysis (Hb < 0.994 mmol/L or < 1.6 g/dL), lipemia (Intralipid < 2000 mg/dL) and biotin (< 205 nmol/L or < 50 ng/mL).

Criterion: Correct assignment of negative and positive samples.

Samples should not be taken from patients receiving therapy with high biotin doses (i.e. > 5 mg/day) until at least 8 hours following the last biotin administration.

No interference was observed from rheumatoid factors up to a concentration of 2300 IU/mL.

No false negative result due to high-dose hook effect was found with the Elecsys HIV combi assay.

In vitro tests were performed on 17 commonly used pharmaceuticals. No interference with the assay was found.

In rare cases, interference due to extremely high titers of antibodies to analyte-specific antibodies, streptavidin or ruthenium can occur. These effects are minimized by suitable test design.

For diagnostic purposes, the results should always be assessed in conjunction with the patient's medical history, clinical examination and other findings.

A negative test result does not completely rule out the possibility of an infection with HIV. Serum or plasma samples from the very early (pre-seroconversion) phase or the late phase of HIV infection can occasionally yield negative findings. Yet unknown HIV variants can also

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lead to a negative HIV finding. The presence of HIV antigen or antibodies to HIV is not a diagnosis of AIDS.

Limits and ranges

Detection limit: ≤ 6 U/mL

The stated sensitivity was determined by reading off the HIV Ag concentration corresponding to the signal of the cutoff value from standard curves obtained by serial dilutions of the Human Immunodeficiency Virus Type 1 (HIV-1 p24 Antigen) - 1st International Reference Reagent 1992, code 90/636 - in human HIV-negative serum.

HIV-1 p24 antigen standard material (NIBSC)		
	COI	U/mL
Standard 1	0.295	0.5
Standard 2	0.387	1.0
Standard 3	0.679	2.5
Standard 4	1.14	5.0
Standard 5	1.63	7.5
Standard 6	2.06	10.0
Cutoff sensitivity	4.2 U/mL	

Reading off the HIV Ag concentration corresponding to the signal of the cutoff value from standard curves obtained by serial dilutions of the HIV-1 p24 antigen (standardized against DuPont, Cat. No. NEA 522001, lot 32286) in human HIV-negative serum a sensitivity of ≤ 33 pg/mL can be stated.

Antibody detection

No international accepted standard for HIV-specific antibody detection exists.

Specific performance data

Representative performance data on the analyzers are given below. Results obtained in individual laboratories may differ.

Precision

Precision was determined using Elecsys reagents, human sera, and controls.

Elecsys 2010 and **cobas e** 411 analyzers						
	Repeatability[b]			**Intermediate precision**[c]		
Sample	Mean COI	SD COI	CV %	Mean COI	SD COI	CV %
HS[d], negative	0.197	0.007	3.4	0.211	0.021	10.1
HS, positive for anti-HIV-1	58.9	0.715	1.2	59.5	2.12	3.6
HS, positive for anti-HIV-2	52.5	0.530	1.0	52.8	2.05	3.9
HS, positive for HIV Ag	11.9	0.111	0.9	11.9	0.426	3.6
PC[e] HIV combi 1	0.246	0.014	5.8	0.240	0.019	7.9
PC HIV combi 2	11.7	0.114	1.0	11.5	0.170	1.5
PC HIV combi 3	14.8	0.219	1.5	14.9	0.417	2.8

b) Repeatability = within-run precision (n = 21)

c) Intermediate precision = between-run (n = 10)

d) HS = human serum

e) PC = PreciControl

MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602 analyzers						
	Repeatability[f]			**Intermediate precision**[g]		
Sample	Mean COI	SD COI	CV %	Mean COI	SD COI	CV %
HS, negative	0.121	0.008	6.5	0.141	0.021	14.8
HS, positive for anti-HIV-1	44.7	0.637	1.4	46.0	2.06	4.5
HS, positive for anti-HIV-2	42.8	0.715	1.7	43.3	1.96	4.5
HS, positive for HIV Ag	10.3	0.303	2.9	10.5	0.563	5.4
PC HIV combi 1	0.157	0.018	11.6	0.173	0.021	12.4
PC HIV combi 2	14.1	0.503	3.6	14.3	0.843	5.9
PC HIV combi 3	11.6	0.175	1.5	11.9	0.515	4.3

f) Repeatability = within-run precision (n = 21)

g) Intermediate precision = within-laboratory (modified protocol (EP5-A) of the CLSI (Clinical and Laboratory Standards Institute): 6 times daily for 10 days (n = 60)

Analytical specificity

1364 samples containing potentially interfering substances were tested with the Elecsys HIV combi assay comprising specimens:

- containing antibodies against HAV, HBV, HCV, HTLV, CMV, EBV, HSV, Rubella, Toxoplasma gondii, Treponema pallidum, Borrelia
- containing autoantibodies and elevated titers of rheumatoid factor
- positive for Candida, E. coli, Enterococci, Plasmodium falciparum/vivax, Mycobacterium tuberculosis
- after vaccination against HAV, HBV, and influenza
- from patients with monoclonal gammopathy and multiple myeloma/lymphoma

	N	Elecsys HIV combi assay RR[h]	Confirmed positive/indeterm. Western Blot (WB)[i]	WB negative, HIV Ag negative
Specimens containing potentially interfering substances	1364	22	12	10[j]

h) RR = repeatedly reactive

i) Samples with indeterminate WB were excluded from calculation

j) Patients with autoantibodies: 2 out of 225; HBV recovered/vaccinated: 2 out of 48; EBV positive: 1 out of 43; HTLV positive: 1 out of 142; T. pallidum positive: 1 out of 38; P. falciparum/vivax positive: 3 out of 137

Clinical sensitivity

Of 179 HIV antigen positive samples from early seroconversion phase, 170 samples were found positive with the Elecsys HIV combi assay. Of 1509 samples from HIV infected patients in different stages of the disease and infected with HIV-1 group M, O and HIV-2, 1509 were found to be repeatedly reactive with the Elecsys HIV combi assay. The sensitivity of the Elecsys HIV combi assay in this study was 100 %. The 95 % lower confidence limit was 99.80 %.

Group	N	Reactive
HIV-1 infected persons from various stages of disease	572	572
Infection with HIV-1 group M (subtypes A-J)	469	469
Infection with HIV-1 group O	13	13
Infection with HIV-2	364	364

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Group	N	Reactive
HIV Ag positive specimens	91	91

60 lysates of cell culture supernatants including different HIV-1 group M subtypes (A-H), HIV-1 group O, and HIV-2 were tested and found reactive in the Elecsys HIV combi assay.

Clinical specificity

In a group of 8406 randomly selected blood donors from Europe and Asia the specificity of the Elecsys HIV combi assay was found 99.76 % (RR). The 95 % lower confidence limit was 99.65 %. In a group of 4389 samples from unselected daily routine, dialysis patients and pregnant women the specificity of the Elecsys HIV combi assay was found 99.63 % (RR). The 95 % lower confidence limit was 99.42 %.

	N	Elecsys HIV combi assay IR[k] COI ≥ 1	Elecsys HIV combi assay RR COI ≥ 1	Western Blot confirmed pos./indeterm.[l]
Blood donors	8406	31	29	6/4
Unselected samples from daily routine	3810	33	34	17/3
Dialysis patients	242	2	2	0
Pregnant women	337	1	1	0

k) IR = initially reactive

l) Samples with indeterminate WB were excluded from calculation

Seroconversion panels

Seroconversion sensitivity of the Elecsys HIV combi assay has been shown by testing 93 commercial seroconversion panels in comparison to registered HIV combi assays or Anti-HIV immunoassays and/or HIV Ag assays.

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For further information, please refer to the appropriate operator's manual for the analyzer concerned, the respective application sheets, the product information and the Method Sheets of all necessary components (if available in your country).

A point (period/stop) is always used in this Method Sheet as the decimal separator to mark the border between the integral and the fractional parts of a decimal numeral. Separators for thousands are not used.

Symbols

Roche Diagnostics uses the following symbols and signs in addition to those listed in the ISO 15223-1 standard.

CONTENT	Contents of kit
SYSTEM	Analyzers/Instruments on which reagents can be used
REAGENT	Reagent
CALIBRATOR	Calibrator
→	Volume after reconstitution or mixing

CE 0123

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